they are implemented too late during the time course/ progression of the somatic illness. Our own findings from a large population based study not only show significant associations of depression subtypes with coronary heart disease but also demonstrate a major role for somatic comorbidity, that has as yet been neglected. If, at all, antidepressive treatments are expected to have an influence not only on depressive symptoms, but also on the progression of a chronic and complex somatic disorder, they probably must be implemented as early and as powerful as possible.

S-52-03

Major depression in the general hospital: Critical appraisal of different strategies to improve its treatment at the University Hospital of Lausanne

A. Berney, L. Michaud, R. Voellinger, B. Burnand, F. Stiefel. *Lausanne, Switzerland*

Objective: Major Depressive Disorders (MDD) remains under-treated in the general hospital despite a high prevalence, major impact on health, and effective therapeutic possibilities; no consensus exists to date as to what strategies would be effective to improve this situation.

Methods: Over the past few years, several efforts targeting MDD were conducted at Lausanne University Hospital: i) a general agenda was established, identifying major difficulties in the management of MDD in the physically ill (1), ii) studies aimed at demonstrating the importance of MDD in specific clinical settings, (i.e. post-stroke depression, Parkinson disease patients) were conducted (2), iii) clinical practice guidelines for the management of MDD in the general Hospital were developed (3) and iv) implementation of guidelines in different somatic services were evaluated.

Results: Preliminary evaluation of the impact of the guideline approach shows very limited effects of a minimal implementation intervention. Focused studies conducted in the service of neurology, seem to be followed by greater changes in clinical practice, with the limit to be circumscribed to very specific settings.

Conclusion: There is a dilemma between the feasibility of large scales brief interventions and time consuming, highly adapted interventions. The minimal requirement for an intervention to improve the management of depression in the General Hospital is an unresolved issue that will be discussed-where possible-by means of scientific evidence. References: 1) Stiefel F et al. Journal of Supportive Care in Cancer (2001), pp: 477-88 2) Berney A et al. Neurology (2002), pp: 1427-29 3) Voellinger R et al. Gen Hospital Psychiatry (2003), pp: 185-193

Tuesday, April 5, 2005

S-53. Symposium: Sleep deprivation: Neurobiological basis and therapeutic aspects

Chairperson(s): Ulrich Hemmeter (Marburg, Germany), Dieter Riemann (Freiburg, Germany)
14.15 - 15.45, Gasteig - Lecture Hall Library

S-53-01

Daytime microsleep, GABAergic mechanisms and neuroendocrine secretion in relation sleep deprivation response in patients with major depression

U. Hemmeter, M. Hatzinger, E. Seifritz, E. Holsboer-Trachsler. *Department of Pscychiatry, Uni, Marburg, Germany*

Objective: Sleep deprivation (SD) has an antidepressive, but temporary efficacy in 60% of depressed patients. Characteristic sleep EEG alterations of depression are improved after SD in the recovery night due to an increase of NonREM sleep pressure. Naps and short sleep-episodes (microsleep) during extended wakefulness reduce NonREM sleep pressure in the recovery night. Furthermore, early morning naps and microsleep during SD can prevent the antidepressant effect of sleep deprivation. The GABA-A-benzodiazepine receptor antagonist flumazenil reduces daytime sleep and increases vigilance. In addition, flumazenil is able to suppress NonREM sleep pressure and NonREM sleep associated growth hormone secretion in early morning recovery sleep after SD in healthy subjects, which is the critical time for a detrimental effect of microsleep and naps on sleep deprivation response.

Methods: Therefore, 27 patients with major depression were subjected to a partial sleep deprivation (PSD). In a double blind randomized design either flumazenil or placebo was orally applied during the initial hours of PSD. A Sleep-EEG was registered continuously for 60 hours by a portable device.

Results: Flumazenil significantly suppressed microsleep during PSD. In the recovery night sleep continuity and slow wave sleep were increased and stage 1 reduced in patients treated with flumazenil compared to placebo. Antidepressant efficacy of PSD was not different between flumazenil and placebo during PSD, but better after the recovery night in patients treated with flumazenil.

Conclusion: It is concluded that GABAergic mechanisms are substantially involved in the regulation of MS and NonREM-sleep during PSD and may be associated with the antidepressant efficacy of PSD.

S-53-02

Sleep deprivation in depression: Involvement of the Renin-Angiotensin-Aldosteron system?

H. Murck, M. Uhr, M. Ziegenbein, H. Kuenzel, K. Held, I. Antonijevic. *Laxdale Limited, Medical Direc, Stirling, United Kingdom*

Objective: Changes in the activity of the renin-angiontensin-aldosterone system (RAAS) in depression have recently been reported. Renin and aldosterone secretion are coupled to sleep in healthy subjects. As total sleep deprivation (TSD) leads to a rapid mood improvement in patients with depression it is of interest to investigate its effect on the response of the RAAS in this population. Additionally we explored HPA-system and the sleep-EEG-changes.

Methods: We compared the sleep related activity of the RAAS before and after TSD in seven depressed patients. After an accommodation night a polysomnographic examination was performed between 23.00 h and 7.00 h. This was followed by 40 h of TSD and the second polysomnography. During the examination nights blood samples were taken every 20 min for analysis of renin, aldosterone, ACTH and cortisol.

Results: During recovery-sleep renin was significantly increased ($p<0.05$). Aldosterone showed no change. ACTH and cortisol were decreased by trend in the first half of the night. REM-density and intermittent wakefulness was significantly decreased ($p<0.05$), whereas slow wave sleep increased by trend in the first half of the night.

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Conclusion: TSD in patients with depression leads to an activation of the RAAS in the recovery night.

S-53-03

HPA system and neurosteroid regulation in relation to sleep deprivation in major depression

C. Schüle, T. Baghai, P. Zwanzger, D. Eser, C. Nothdurfter, R. Rupprecht. *University of Munich LMU, Clin, Munich, Germany*

Objective: In the present investigation, the hypothalamic-pituitary-adrenocortical (HPA) axis activity (study 1) and concentrations of neuroactive steroids (study 2) were measured in depressed patients treated with partial sleep deprivation (PSD).

Methods: 39 (study 1) and 29 (study 2) drug-free patients suffering from major depression (DSM-IV criteria) were treated with PSD. PSD response was defined as a reduction of at least 30% according to the 6-item version of the Hamilton-Depression Scale (6-HAMD). HPA axis activity was measured using the dexamethasone/CRH test (study 1). In study 2, plasma samples were taken the day before and after PSD and after one night of recovery sleep at 8:00 AM for quantifying neuroactive steroids (combined gas chromatography/mass spectrometry analysis).

Results: In study 1, patients with postdexamethasone cortisol levels < 15 ng/ml (before CRH administration) showed a significantly greater 6-HAMD score reduction after PSD than patients did with postdexamethasone cortisol > 15 ng/ml. Moreover, a significant negative correlation between postdexamethasone cortisol and 6-HAMD score reduction was demonstrated. In study 2, there was no influence of PSD on the concentrations of neuroactive steroids neither in PSD responders nor in non-responders. However, non-responders showed significantly higher concentrations of 3alpha,5alpha-tetrahydroprogesterone (3alpha,5alpha-THP), 3alpha,5beta-tetrahydroprogesterone (3alpha,5beta-THP), and dehydroepiandrosterone (DHEA) before or after PSD compared to responders.

Conclusion: Apparently, HPA axis activity and the concentrations of certain neuroactive steroids are associated with response to PSD. However, in contrast to antidepressant drugs which correct the dysequilibrium of neuroactive steroids in major depression within several weeks, PSD does not affect the concentrations of neuroactive steroids neither in responders nor in non-responders.

S-53-04

The role of brain monoamines in the antidepressant response to sleep deprivation

F. Benedetti, B. Barbini, A. Bernasconi, M. Cigala Fulgosi, C. Colombo, S. Dallaspezia, A. Pontiggia, E. Smeraldi. *Università Vita-Salute San Raf, Milano, Italy*

Combined treatment of bipolar depression with lithium salts, antidepressant drugs, and chronobiological inteventions such as single or repeated total sleep deprivation (TSD), sleep phase advance (SPA), and morning light therapy (LT), allowed to reach response rates of 60-70% and could successfully prevent relapse, thus providing clinical psychiatrists with new instruments to achieve rapid and sustained antidepressant response in bipolar depressed patients. The synergist combination of chronotherapeutic treatments and drug enhancing the activity of brain monoamines suggested common mechanisms of action. In the last years data from genetic research allowed to partially explain the mechanism of action of chronobiological treatments. The influence of a functional polymorphism in the transcriptional control region upstream of the coding sequence of the 5-hydroxytryptamine transporter (5-HTTLPR) on response to TSD was found to be similar to that observed on response to serotonergic drug treatments. Patients treated with TSD followed by light treatment showed the same influence of 5-HTTLPR. Finally, preliminary recent observations suggested that variants of genes pertaining to the molecular clock (CLOCK and GSK3-) influence core features of the illness such as age at onset and recurrence of illness, and response to TSD and lithium salts.

S-53-05

Therapeutic efficacy of sleep deprivation and other sleep-wake-manipulations in major depression

D. Riemann. *Universitätskrankenhaus Klinic für Psychiatrie, Freiburg, Germany*

Objective: It has been demonstrated convincingly, that a night of total sleep deprivation leads to an immediate and swift amelioration of mood in approximately two thirds of patients with a major depression who are subjected to the procedure. Unfortunately, the effect of sleep deprivation is short lived and usually after the next night of sleep the majority of patients relapse into depressed mood. Insofar, total sleep deprivation has always been seen as an adjunct therapy, in order to shorten the time lag between initiation of antidepressant pharmaco- or psychotherapy and the onset of action of these kind of therapies.

Methods: Own studies focused on the question, whether it is possible to prolong the short lived effect of sleep deprivation by other sleep-wake-manipulations. In our strategy, after sleep deprivation patients were subjected to a phase advance of sleep time. Initially, patients were allowed to sleep from 17.00 to 24.00 hours and then bedtime was graduately shift back to the normal phase on one hour per day until the normal phase position was reached.

Results: In several studies it was shown that with this procedure approximately two thirds of patients who respond to sleep deprivation can be stabilized in their mood state as experienced directly after sleep deprivation. This was shown in medicated and unmedicated patients and also in a controlled design where one half of the patients was subjected to phase advance and the other half to phase delay. In the most recent study we were also able to replicate our results with a shortened period of only 3 days of sleep phase advance after sleep deprivation.

Conclusion: It has also been shown for sleep deprivation and partial sleep deprivation, combined sleep deprivation and light therapy and combined regimes of sleep deprivation and medication that it is possible to sustain the positive effect of sleep deprivation at least in subsamples of depressed patients.

Tuesday, April 5, 2005

S-58. Symposium: Placebo-controlled studies for the research of new antidepressant drugs: Necessary, ethical and feasible?

Chairperson(s): David Baldwin (Southhampton, United Kingdom), Siegfried Kasper (Wien, Austria)
16.15 - 17.45, Gasteig - Philharmonie

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